

# FEDEROFF DECLARATION

## Exhibit J

## Therapeutic Stereotactic Procedures on the Thalamus for Motor Movement Disorders

J. Siegfried

AMI Klinik Im Park, Zürich, Switzerland

### Summary

The value of functional neurosurgery in the treatment of motor movement disorders is emphasized. The two methods of stereotactic procedures, namely a destructive one with small lesions centered on specific targets, and a non-destructive one with chronically inserted electrodes connected with an also implanted programmable neuro-pacemaker are described in detail. The results in Parkinsonian tremor, essential tremor, tremor of multiple sclerosis, post-traumatic tremor and in other involuntary movement disorders are reported and demonstrate that stereotactic neurosurgical treatment of these conditions is a safe and efficacious method.

**Keywords:** Motor movement disorders; tremor; Parkinson's disease; thalamotomy; deep brain stimulation.

Two methods of stereotactic procedures can be used in the therapeutic control of motor movement disorders: a destructive one with small lesions centered on specific targets and a non-destructive one with chronically inserted electrodes connected with an also implanted programmable neuropacemaker.

### I. Stereotactic Deep Brain Lesions

Since the introduction of stereotactic brain operations in man in 1947, most surgical efforts to improve abnormal movements and dystonic conditions have focused on localized destruction of various parts of the thalamus, mesencephalon, and cerebellar nuclei. Many types of movement disorder were treated by this technique which allows for localizing, stimulation, and destroying specific subcortical parts of the brain without damaging the overlying brain structures, thus alleviating diseases which had previously been difficult or impossible to treat. This method of treatment became particularly popular in the mid 1950', when it was proved that stereotactic destruction of the ventrolateral

nucleus of the thalamus suppresses tremor and rigidity in Parkinson's disease and tremor of other origins in the contralateral side in a very high percentage of cases without producing clinically detectable neurological deficits. The stereotactic methods and frames used for this interruption of the pallido-thalamo-cortical pathway are many, but they are all based on the same principle of combining radiography, atlas measurements, and physiological techniques to aid in localizing the target point. The lesion may be produced mechanically, chemically, or electrically, the last one being the most reliable.

### 1. Technique

Our own technique, using the Riechert-Munding frame, stereotactic ventriculography, intracerebral stimulation to localize the target in the thalamus and high-frequency electrocoagulation to produce the lesion, will be described.

During placement of the frame and subsequent surgery, only local anaesthesia is used. Patients with multiple sclerosis receive corticosteroids one day before surgery, but no other premedication or antibiotics are given routinely. The patient is wide awake, fully co-operative and his involuntary movements are not modified during the procedure, while the patient is in a supine position and the frame in place, a lateral roentgenogram is obtained. A line is drawn on the film from bregma to dorsum sellae, and the length of the line is measured and then multiplied by a constant factor of 0.6874. The resulting figure becomes a distance that is measured along the reference line on the roentgenogram, beginning at the bregma. The target for the ventricular needle is a point 3 mm posterior to this point along the bregma-dorsum sellae line<sup>25</sup>. This method of localizing the foramen of Monro is successful in 95% of cases. Using a 2.5 mm drill, a burr hole is made without an incision in a small area of shaved scalp at a point approximately 2 cm anterior to the coronal suture and 3 cm from the midline. After coagulation of the dura, the cannula is inserted, 7–8 cm<sup>3</sup> of cerebrospinal fluid is removed, and 15–20 cm<sup>3</sup> of air is injected; sufficient filling of the third ventricle

and usually, the aqueduct and the fourth ventricle is obtained. The nucleus V. im., target for tremor, is located along the foramen of Monro-posterior commissure reference line, generally 7 to 11 mm in front of the posterior commissure when the line measures 23.5 mm, and 11 mm lateral to the third ventricle border. After this calculations are determined, an identical burr hole is made and an electrode of 2 mm diameter with a 2 mm exposed tip containing also inside a second 0.7 mm electrode, which has the capability of lateral extension controlled by a micromanipulator, is introduced. The anatomical placement of the electrode is confirmed by 1–130 Hz stimulation using biphasic wave forms of 1–2 msec duration. Such stimulation enables us to identify the internal capsule as well as points at which the tremor is arrested (over 100 Hz), initiated, or facilitated (up to 50 Hz). For surgical procedures on the dominant side, it allows us to observe the effect of stimulation on speech. Next, a lesion is made, while the patient is observed for evidence of weakness or other untoward effects. The size of the lesion is increased until the tremor is absent even with facilitated measures, unless, of course, weakness or dysphasia occurs. If the lesion must be made outside the axis of the electrode pass, extension of the string electrode laterally or posteriorly with the micromanipulator is invaluable, for it obviates the need for another electrode pass. Using the computer-calculated target points, we are able to perform the entire operation in one stage in 60 to 70 minutes. The patient is transferred back to the room fully alert and is usually discharged in fewer than six days.

## 2. Results

*a) Parkinson's:* This method has been used by us in more than 1,800 patients. We have found it to be successful in 85% of the cases in which it was performed for unilateral tremor and have had similar results with rigidity. Transient postoperative contralateral facial paresis, lateropulsion, and foot-dragging were seen in 30% of closely monitored patients, but these side effects lasted only a few days to a few weeks. In 10% of patients who had surgery in the dominant hemisphere, dysphasia appeared and was usually longer lasting<sup>21, 23, 24</sup>. These results have also been examined in patients over 70 years of age. They were the same and the incidence of complications was not higher. The only significant difference is that the elderly patients were hospitalized longer, for both social and rehabilitative reasons<sup>22</sup>.

When patients were observed closely for learning and memory changes following thalamotomy, we found that the left-sided lesions affected mainly verbal memory and that right-sided lesions affected non-verbal memory. These alternations, however, were limited in content and duration, and did not affect attention span or short-term memory<sup>15</sup>. In our series, the perioperative mortality rate was 0.2%. In bilateral procedures, even with an interval of at least one year between the two operations, speech, balance and swallowing difficulties developed in 20% of patients after a lesion was placed on the second side. For this reason,

since 1987, we have generally proposed the chronic implantation of a thalamic electrode connected with a neuromodulator for the second side. However, in a long follow-up of 55 cases of Parkinson's disease operated on bilaterally, it has been suggested by Tasker that bilateral thalamotomy may retard the progress of the disease<sup>16</sup>.

*b) Essential (familial) tremor:* The same target point for the stereotactic procedure as described above gives the same rate of success for essential tremor as for the tremor of Parkinson's disease. However, a single small coagulation is rarely sufficient for an optimal result; the volume of the lesion may be larger in many cases than is necessary for Parkinsonian tremor. A success rate approaching 96% is given by Riechert<sup>20</sup>. However, even if the intention tremor disappears completely without slight paresis, some dyspraxia of the hand can be observed, in 10% of patients of our own series of 629 cases published in 1983<sup>27</sup>. Only rehabilitation will permit the patient to use his hand normally.

*c) Tremor of multiple sclerosis:* In contrast to essential tremor, the intention tremor of multiple sclerosis does not demonstrate a regular rhythm and is often accompanied by ataxic movements with dysmetria. Treatment by stereotactic operation is based on the same principles as used for Parkinson's syndrome. Riechert mentions 65.5% very good results, which corresponds also to our observations in more than 100 cases operated upon. Even if the tremor can be cured in 80% of the cases, the ataxic movements will not be influenced, thus the functional result of the operation is satisfactory only in 65.5% of the cases. Hydrocephalus is often marked in advanced multiple sclerosis so that the calculation of the target point is less precise and the complication of hemiparesis more frequent. A CT examination prior to the operation is desirable.

*d) Post-traumatic tremor:* Although mentioned only exceptionally in the literature, the post-traumatic intention tremor is a very good indication for stereotactic thalamotomy and in the last 20 years, we have operated on 24 cases. The majority of them were children or young adults who had severe brain injury after a traffic accident. After a period of days to months of coma, the initial neurological deficit of dense hemiparesis showed progressive improvement which was accompanied by a slowly increasing tremor of cerebellar type. All cases showed a marked to very marked improve-

ment of the tremor and a large increase of functional ability postoperatively. In their series of 14 cases, Bullard and Nashold came to the same conclusion<sup>11</sup>.

*e) Chorea-athetosis and other involuntary movements:* In the 1960s stereotactic thalamotomies for choreo-athetosis, torticollis spasmodicus, and other hyperkinesias besides tremor were thought to be beneficial. However, over the years, these operations lost their popularity, and are practically no longer performed, since the long-term results in functional improvement are not particularly satisfactory. The only exception is the indication for iatrogenic involuntary movements observed under L-Dopa treatment. Since 1975 we have performed successfully stereotactic thalamotomies for iatrogenic dyskinesias, when these movements are marked on one side of the body with an otherwise satisfactory medical therapy of akinesia. The good results, also with pain relief, permit a sufficient L-Dopa dosage for optimal efficacy without marked dyskinetic movements as side-effects.

## II. Stereotactic Deep Brain Stimulation

The first modern application of chronic therapeutic deep brain stimulation in human motor movement disorders appeared in several articles by Bechtereva and the colleagues between 1972 and 1975<sup>2-4</sup>. They reported that chronic stimulation had favourable effects in patients who had tremor associated with Parkinson's disease, Wilson's disease, and dystonia musculorum deformans. Unfortunately, information regarding the number of patients, the techniques for electrode placement, and the proposed target was not divulged.

Mundinger was the first to describe in detail beneficial effects on abnormal motor behaviour when chronic stimulation was performed in specified deep brain areas, such as the thalamus, pulvinar, and dentate nucleus<sup>18</sup>. In a 1982 review of patients with dystonia, spasticity, and spasmodic torticollis, Mundinger emphasized the importance of stimulation-induced paraesthesias overlying the affected area<sup>19</sup>.

Brice and McLellan reported suppression or decrease of severe intention tremor in three females with multiple sclerosis by stimulation of the subthalamic region (20 mm behind the anterior commissure, 6–8 mm below the intercommissural plane, and 10 mm from the midline)<sup>10</sup>. The sensory thalamic ventroposterolateral nucleus was stimulated by Mazars to alleviate deafferentation pain; they found that stimulation also controlled associated abnormal movements<sup>17</sup>. He stressed

the significance of stimulation-induced paraesthesias affecting the involved portion of the body. Cooper has reported the largest series of patients with involuntary movement disorders treated by deep brain stimulation. In a group of 49 patients of various types of disorders and causes, he stimulated the posterior thalamus, internal capsule, and zona incerta; 27 were improved<sup>13, 14</sup>. The thalamic area surrounding the ventral intermediate nucleus (V. im.), the centromedian (CM), and the parafascicular nucleus (PF) were stimulated in 9 patients by Andy<sup>1</sup>. The motor problems in these patients consisted of congenital, traumatic, or Parkinsonian tremor, torticollis, and facial spasm. He reported the results in six patients as good to excellent and in three patients (with Parkinsonian tremor) as fair to good. We have reported in 1986 four cases of thalamic pain syndrome presenting with marked abnormal dyskinetic movements and two cases of very strong spasticity due to traumatic paraplegia who received thalamic stimulation for deafferentation pain<sup>28</sup>. In all four cases of dyskinesia, stimulation has given satisfactory paraesthesias in the painful area and suppressed almost instantly the involuntary movements associated with the thalamic pain syndrome. In two cases of paraplegic pain associated with significant lower extremity spasticity, the stimulation of the sensory thalamic nucleus suppressed almost instantly the clonus of the contralateral leg. Benabid implanted in 1987<sup>5</sup> a stereotactic stimulation device in the ventrolateral part of the thalamus (V. im.) to control Parkinsonian tremor with good results, like we did in the same year.

### 1. Technique

The stereotactic technique and the co-ordinates for the nucleus V. im. have been described above.

Our coordinates for the thalamic sensory nuclei (VPL) are the following: for the upper extremities: 3 mm in front of the posterior commissure, 1 to 2 mm below the baseline and 13 mm laterally to the midline. For the lower extremities, the laterality to the midline is 16 mm. A very smooth, flexible electrode of 1.3 mm diameter with a central rigid stylet is used. The stimulating tip has a surface of 7 mm<sup>2</sup>. High resistance to fatigue fracture is provided by the helical design of the electrode wire. This form makes the electrode highly flexible and allows it to move with the brain. Another important feature of the electrode is that it has virtually no resilience which allows the electrode to remain bent upon stylet removal. A screw made with pure titanium, highly biocompatible material in bone, has been designed to secure the electrode in a burr-hole of 2.5 mm before the stylet is removed and it provides a water-tight seal of the burr-hole<sup>25</sup>. When the tremor or other involuntary movements are satisfactorily controlled, a programmable neuromodulator is implanted in a subcutaneous pocket in the infraclavicular region and connected subcutaneously with the deep brain electrode.

## 2. Results

a) *Tremor*: Parkinsonian tremor can be suppressed with continuous stimulation of 130 Hz in practically all cases according to Benabid<sup>6</sup>; this is also true for other types of tremor<sup>7</sup>. In his last publication<sup>8</sup>, Benabid reports in a series of 43 thalami stimulated (32 patients) complete relief from tremor in 27 and major improvement in 11 (88%). In our own experience since 1987, we reported in a co-operative study with Blond<sup>9</sup> a total suppression of tremor during the stimulation with 130 Hz in 12 of 19 cases of Parkinsonian tremor operated on. In 7 cases, the tremor was only partially controlled. In 2 cases of essential tremor, only one has been suppressed. In 10 cases of the whole series, a massive rebound of tremor when the stimulation is arrested has been observed. Foot dystonia in 2 cases, dysarthria in 1 case and lateropulsion in another case were the reversible side-effects. With our own series of 36 patients up to 1991, we can confirm that tremor can be perfectly well controlled with this method in 65% of cases.

As an alternative in the neurosurgical treatment of tremor, we consider the chronic thalamic stimulation as the indication of choice when the risk of high frequency coagulation is high (pre-existing speech disturbances, psycho-organic syndrome) and for the opposite side after successful thalamotomy for one side (Table 1). The disadvantages of chronic stimulation cannot be ignored; with two operations, the hospitalization of the patient is longer, the risks of infection and reject reaction exist and the cost of the device which has to be replaced about every 3–4 years, are limiting factors.

b) *Other abnormal involuntary movements*: In 2 cases of other abnormal involuntary movements, Benabid reports significant improvement only for 1 to 6 months during chronic V. im. stimulation<sup>7</sup>. When involuntary

movements are associated with sensory disturbances, we obtained good results with the stimulation of the sensory nucleus (VPL) somatotopically to the projection of the abnormal movements.

## III. Conclusion

Thirty years ago, Cooper wrote: "At the present time there is no medicinal agent which can cure any single component of the Parkinsonian syndrome. There is no medicinal agent which can halt the progress of the disease or reverse tremor, rigidity, or deformity associated with the Parkinsonism".<sup>12</sup> This sentence for many patients is still true, but only as far as tremor is concerned for the majority of them. Stereotactic procedures, thalamotomies and/or thalamic stimulation is a successful therapy for at least two manifestations – tremor and rigidity. Neurosurgical treatment of all kinds of tremor, and also of rigidity and iatrogenic dyskinesias is still a safe and efficacious method, and must be discussed when these symptoms incapacitate the function and social life of the patient. Although it is generally stated that medicinal therapy should be given on adequate trial before surgical intervention is advised, such a sequence may be correct in certain cases, with the exception of the Parkinson's disease; when the patient shows a moderate tremor of any origin, the surgeon's electrode may be less costly and less toxic than the physician's pills. As has been said for epilepsy, drug therapy has many drawbacks. It is a tedious and troublesome form of treatment which usually must be continued for an indefinite period; it can have unpleasant side-effects, and it is at best a form of control, not a cure. Stereotactic procedure may control the tremor quicker and better for the whole of life than does drug therapy.

Table 1. Stereotactic Procedures and Target Points Proposed in the Treatment of Motor Movement Disorders

<i>Tremor</i>	
One side, no risks	V. im. coagulation
One side: speech disturbances, psycho-organic syndrome	V. im. stimulation
Opposite side (later on)	V. im. stimulation
<i>Involuntary movements</i>	
With sensory disturbances	VPL stimulation
<i>Dystonia, spasticity</i>	
With sensory disturbances	VPL stimulation

## References

1. Andy OJ (1983) Thalamic stimulation for control of movement disorders. *Appl Neurophysiol* 46: 107–111
2. Bechtereva NP, Bondartchek AN, Smirnov VM, *et al* (1972) Therapeutic electrostimulation of the deep brain structures. *Vopr Neurokhir* 1: 7–12
3. Bechtereva NP, Bondartchek AN, Smirnov VM, *et al* (1975) Method of electrostimulation of deep brain structures in treatment of some chronic diseases. *Confin Neurol* 37: 136–140
4. Bechtereva NP, Kombarova DK, Smirnov VM, *et al* (1975) Using the brain's latent abilities for therapy: chronic intracerebral electrical stimulation. In: Sweet WH, *et al* (eds) *Neurosurgical treatment in psychiatry, pain and epilepsy*. University Park Press, Baltimore, pp 581–613
5. Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J (1987) Combined stereotactic surgery of the VIM thalamic nu-

- cleus for bilateral Parkinson's disease. *Appl Neurophysiol* 50: 344-346
6. Benabid AL, Pollak P, Hommel M, Gaio JM, de Rougemont J, Perret J (1989) Traitement du tremblement parkinsonien par stimulation chronique du noyau ventral intermédiaire du thalamus. *Rev Neurol* 145: 320-323
  7. Benabid AL, Pollak P, Louveau A, Hommel M, Perret J, de Rougemont J (1989) Chronic VIM-thalamic stimulation in movement disorders. In: Crossman AR, Sambrook MA (eds) *Current problems in neurology, Vol 9. Neural mechanisms in disorders of movement*. Libbey, New York, pp 393-395
  8. Benabid AL, Pollak P, Gervason C, *et al* (1991) Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus. *Lancet* 337: 403-406
  9. Blond S, Siegfried J (1991) Thalamic stimulation for the treatment of tremor and other motor movement disorders. *Acta Neurochir (Wien) [Suppl]* 52: 109-111
  10. Brice J, McLellan L (1980) Suppression of intention tremor by contingent deep brain stimulation. *Lancet* 1: 1221-1222
  11. Bullard DE, Nashold BS (1988) Posttraumatic movement disorders. In: Lunsford LD (ed) *Modern stereotactic neurosurgery*. Nijhoff, Boston, pp 341-352
  12. Cooper IS (1961) *Parkinsonism, its medical and surgical treatment*, Vol 1. Thomas, Springfield 111, p 239
  13. Cooper IS (1982) A general theory of caution and reversibility of involuntary movement disorders. *Appl Neurophysiol* 45: 317-323
  14. Cooper IS, Upton ARM, Amin I (1982) Chronic cerebellar and deep brain stimulation in involuntary movement disorders. *Appl Neurophysiol* 45: 209-217
  15. Kocher U, Siegfried J, Perret E (1982) Verbal and nonverbal learning ability of Parkinson patients before and after unilateral ventrolateral thalamotomy. *Appl Neurophysiol* 45: 311-316
  16. Li CS, De Carvalho G, Taaker RR (1990) Does VIM thalamotomy affect the course of Parkinson's disease? *Stereotactic Funct Neurosurgery* 54:192
  17. Mazars G, Merienne L, Cioloca G (1980) Control of dyskinesias due to sensory deafferentation by means of thalamic stimulation. *Acta Neurochir (Wien) [Suppl]* 30: 239-243
  18. Mundinger F (1977) Neue stereotaktisch-funktionelle Behandlungsmethode des Torticollis spasmodicus mit Hirnstimulatoren. *Med Klinik* 72: 1982-1986
  19. Mundinger F, Neumüller H (1982) Programmed stimulation for control of chronic pain and motor diseases. *Appl Neurophysiol* 45: 102-111
  20. Riechert T (1980) *Stereotactic brain operations*, Vol 1. Hans Huber, Bern, p 386
  21. Siegfried J (1968) *Die Parkinsonsche Krankheit und ihre Behandlung*, Vol 1. Springer, Wien New York, p 262
  22. Siegfried J, Zumstein H (1976) Thalamotomies stéréotaxiques pour troubles fonctionnels chez les personnes âgées. *Neurochirurgie* 22: 536-539
  23. Siegfried J (1980) Is the neurosurgical treatment of Parkinson's disease still indicated? *J Neural Transm [Suppl]* 16: 195-198
  24. Siegfried J (1980) Neurosurgical treatment of Parkinson's disease. Present indications and value. In: *Parkinson's disease, current progress, problems and management*. Elsevier, North Holland, pp 369-376
  25. Siegfried J, Brandli-Graber S (1980) Repérage radiologique simple du trou de Monro sur les radiographies crâniennes à vide. *Neurochirurgie* 26: 387-389
  26. Siegfried J, Comte P, Meier R (1983) Intracerebral electrode implantation system. *J Neurosurg* 59: 356-359
  27. Siegfried J, Hood T (1983) Current status of functional neurosurgery. In: Krayenbühl H (ed) *Advances and technical standards in neurosurgery*, Vol 10. Springer, Wien New York, pp 19-79
  28. Siegfried J (1986) Effets de la stimulation du noyau sensitif du thalamus sur les dyskinésies et la spasticité. *Rev Neurol* 142: 380-383

Correspondence: Prof. Dr. J. Siegfried, Neurochirurgie, Klinik im Park, Seestrasse 220, CH-8002 Zürich, Schweiz.